LUTEAL PHASE DEFECTS: RECOGNITION AND MANAGEMENT

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THE endocrine causes of female infertility account for approximately 15 to 25% of all cases. The majority of these are anovulatory states. It should be recognized, however, that a significant number of patients with regular menses and no associated anatomical abnormality have a disturbance of ovulatory cycles, resulting in decreased fertility. Further, if pregnancy does occur, there may be increased wastage during the first trimester. In these women there exists a possibility of luteal phase defect. This diagnostic entity implies an impairment of ovarian function, with inadequate secretion of progesterone, leading to the development of an intrauterine environment which is incompatible with the cycle phase.

Significantly, the length of the cycle in such patients will not be markedly disturbed. Only in the most severe form of this ovarian endocrinopathy—aluteal cycles[1]—or in greatly altered luteal performance occurring near the time of the menopause will the duration of the cycle be altered.

Various authors who have discussed defects in the luteal phase estimate its incidence in all infertility patients at 6.7%[2] to 19%.[3] G. E. S. Jones reported that in 550 patients with primary infertility the incidence was 3.7%,[4] whereas in secondary infertility the incidence increased nearly 11-fold.[5]

Rock and Bartlett (1937)[6] seem to have been the first to suggest that inadequate endometrial response might be associated with infertility. Jones[7] in 1949 further discussed this association and pointed out the importance of the endometrial biopsy in the diagnostic study. She felt

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that this procedure was more valuable than other indirect methods of estimating luteal function.

It is quite obvious that abnormal function of the corpus luteum will result in impairment of reproductive performance; deficient output of progesterone affects endometrial decidual reaction, contractility of uterine muscle, and tubal motility. Theoretically ovum transport, localization of implantation, and site of nidation can all be affected. Infertility, wastage of pregnancy, either as "silent" or "occult" abortion, when the fertilized egg is shed with menstrual flow, or first-trimester abortion, result from disturbed correlation between the three aforementioned effects of insufficiency of progesterone.

Theories of etiology suggest either the possibility of primary ovarian dysfunction implying faulty corpus luteum development or, most probably, inadequate release of pituitary luteinizing hormone (LH), which plays a role in the formation of abnormal corpora lutea. As LH causes rupture of the follicle, initial formation of the corpus luteum and production of progesterone, an altered output of LH, should exert a deleterious effect on the postovulatory ovarian response and on steroidogenesis.

Such inadequate release of LH is mediated via the hypothalamus as the result of psychogenic or neurogenic factors, or might result from hypothalamic-pituitary disturbance arising from metabolic, nutritional, or iatrogenic influences. Various drugs such as potent tranquilizers and antihistamines have been implicated in the impairment of neurotransmission by the hypothalamus. Convincing evidence that the central part of the reproductive axis might be responsible for faulty function of the corpus luteum is found in patients undergoing induction of ovulation. The discrepancy between the rates of ovulation and conception, increased wastage of pregnancy, and findings of abnormal endometrial patterns during Clomid therapy[8] point to the central factors as responsible for abnormal ovarian response. It should also be mentioned that decreased output of estrogen during the proliferative phase can prevent full secretory endometrial development after ovulation.

Considering the various etiological factors, luteal deficiency may occur in the form of transient or single episodes; for diagnosis and for therapeutic implications the patient must be observed and the luteal insufficiency noted during repeated cycles.

Evaluation of Luteal Function

1) *Basal body temperature (BBT).* The monthly record of BBT should create a baseline for diagnostic study of the patient and for the timing of other diagnostic tests. BBT alone is a poor index of corpus luteum function, since it tends to give an all-or-none response. Only gross alterations in output of progesterone can be reflected in the BBT curve. More subtle variations in BBT gain significance only when correlated with other clinical parameters. The duration of the luteal phase should be calculated from the low point of the basal body temperature, which represents ovulation, to the onset of subsequent flow. The duration of the follicular phase in any given cycle varies greatly; however, the duration of the luteal phase seems to be constant in most normal human females.

2) *Pregnanediol.* The progesterone molecule is ordinarily reduced in the liver to the many possible epimeric forms of pregnanediol and 16-hydroxy derivatives and excreted as such in conjugated forms. The pregnanediol measured in the conventional urinary assay represents only approximately 20% of secreted progesterone but suffices as a clinical guide to its secretion. The levels of pregnanediol during the normal menstrual cycle are well established; however, they are characterized by wide daily variations, which means that a single determination is not very helpful. Serial determinations which would be necessary for the diagnosis are impractical and costly. Yet if the pregnanediol level established between cycle days 19 to 25 is less than 2 mg./24 hr. it indicates a marked abnormality of corpus luteum function. It should be pointed out at this time that clinical end points of steroid action discussed below are more economical, quicker, and frequently more reliable as to the quantitative and qualitative aspects of progesterone secretion than the biochemical assays presently available.

3) *Cervical mucus.* The cervical mucus arborization test, utilized for evaluation of estrogen secretion and timing of ovulation, cannot be reliably applied to the estimation of postovulatory progesterone output. Arborization does not become clearly negative until several days after ovulation, and there are great individual variations. Ferning phenomenon may persist through normal luteal phase, and it has been reported that a significant number of women can retain this phenomenon during pregnancy.[9]

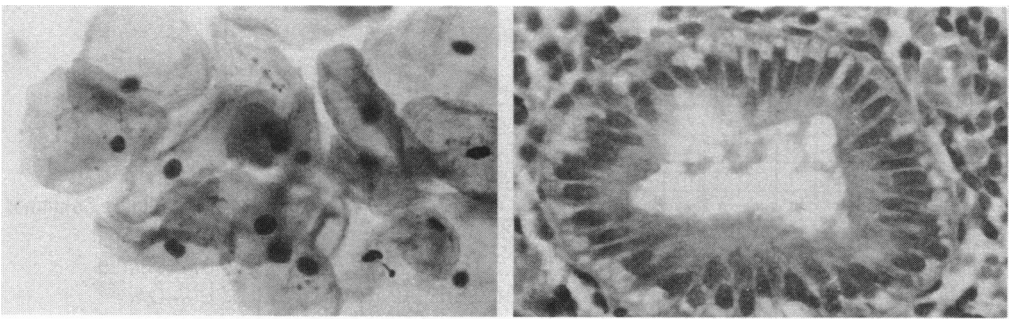

Fig. 1. Assessment of cycle phase by vaginal cytology and simultaneous endometrial biopsy. Progestational smear compatible with histologic diagnosis of cycle day 18.

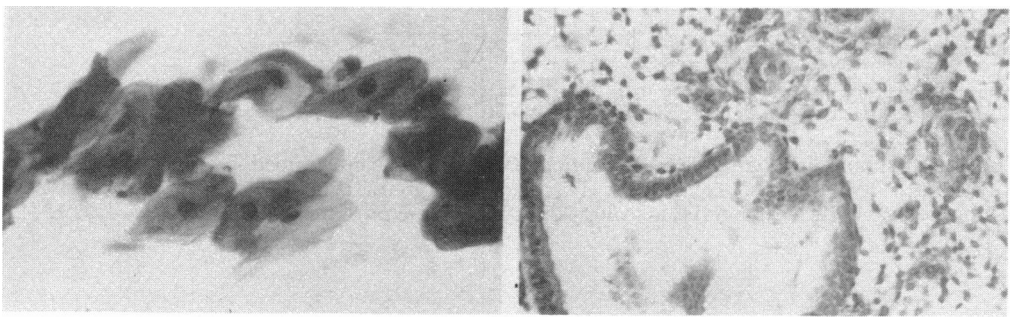

Fig. 2. Assessment of cycle phase by vaginal cytology with simultaneous endometrial biopsy. Progestational smear compatible with histologic diagnosis of cycle day 24.

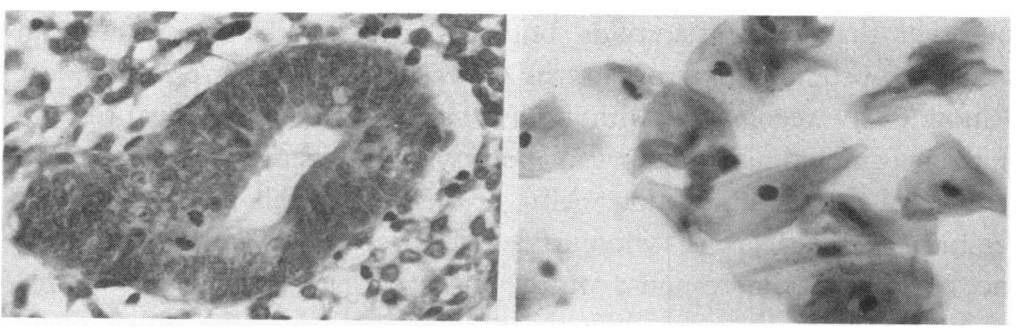

Fig. 3. Assessment of cycle phase by vaginal cytology and simultaneous endometrial biopsy. Progestational smear incompatible with cycle day by history and histologic diagnosis of proliferative endometrium. Pseudoprogestational diagnosis in vaginal cytology possibly produced by fluctuations in preexisting estrogen level.

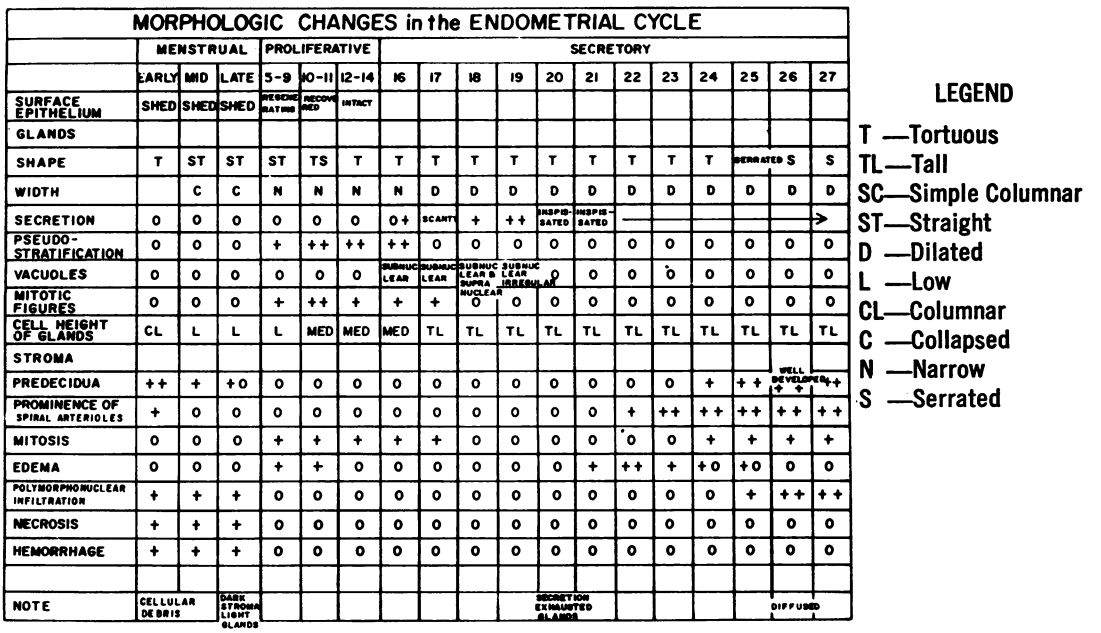

Fig. 4. Morphologic changes in the endometrial cycle. Reproduced by permission from Reyniak, J. V., Sedlis, A., Stone, D., and Rimdusit, P.: Comparison of hormonal colpocytology with endometrial histology in gynecologic patients. *Acta Cytol. 15*:329, 1971.

4) *Vaginal cytology*. This method represents an excellent means for the assessment of the hormonal status of the gynecologic patient, having the additional advantage of being painless and easy to obtain repeatedly. The vaginal mucosa, however, being also a target organ for other than ovarian steroids, both exogenous and endogenous, can sometimes produce bizarre patterns of cytology. The estrogenic smear is most easily recognized, although it can be altered by the presence of nonspecific stimuli which can modify or interfere with the pattern of vaginal-cell desquamation. Also, it has been well established that vaginitis, various drugs, vitamin deficiencies, and metabolic disturbances can alter the response of the target organ. The progestational vaginal cytology is more difficult to interpret, since the luteal phase is a multihormone condition, and a quantitative assessment of progesterone effect may be nearly impossible. Further, progesteronelike patterns of cytology may be imitated by fluctuations in preexisting estrogen levels, or by the influences of other steroids. It takes a great deal of experience to evaluate properly the postovulatory smear, and still,

on occasion, an erroneous conclusion could be reached (Figures 1, 2, and 3).

5) *Endometrial biopsy*. This represents an unsurpassed method of appraisal of ovulation and the function of the corpus luteum. As pointed out before, it is frequently more accurate than biochemical methods involving the recovery of progesterone metabolites. Further, it is biologically more meaningful. While the proliferative phase is impossible to date, the luteal phase is characterized by predictable, constant changes. Endometrial dating can be assessed on the basis of the fundamental observations of Noyes, Hertig, and Rock.[10] Sedlis[11] described in detail the cyclic morphological changes in the endometrium, presented in a table. These data greatly facilitate the determination of the correct endometrial date (Figure 4).

It must be mentioned that accurate dating, which allows the quantitative assessment of luteal performance, does require training and experience frequently above the quality of an average general pathologist. It would be beneficial to every gynecologist with a large infertility practice to learn to evaluate endometrial biopsies.

Secretory changes begin in the endometrium approximately 36 to 48 hours after ovulation, and they progress in a predictable fashion throughout the luteal phase.

The technique of biopsy implies obtaining a full-thickness sample of the endometrium from the fundus, since the lower uterine segment does not reflect cyclic changes. Although the biopsy causes discomfort to the patient, it should never be painful when properly performed with a Novak's or, even better, with a Miles curette. The reduction in discomfort can be achieved by use of a topical anesthetic spray on the exocervix and by placing a cotton-tipped applicator soaked with the same anesthetic solution in the endocervical canal prior to procedure. The timing of the biopsy is most essential, and should be done in accordance with the luteal phase length as timed by BBT and the onset of menses in earlier cycles. Usually the recommended timing on the first day of menstrual flow results in endometrial samples totally unsuitable for quantitative progesterone assessment and only general information about the presence or absence of the effect of this steroid. For evaluation of the infertile patient and diagnosis of luteal phase compatibility, the biopsy should be performed on cycle day 21, which represents the implantation date, or day 26, which reflects the entire

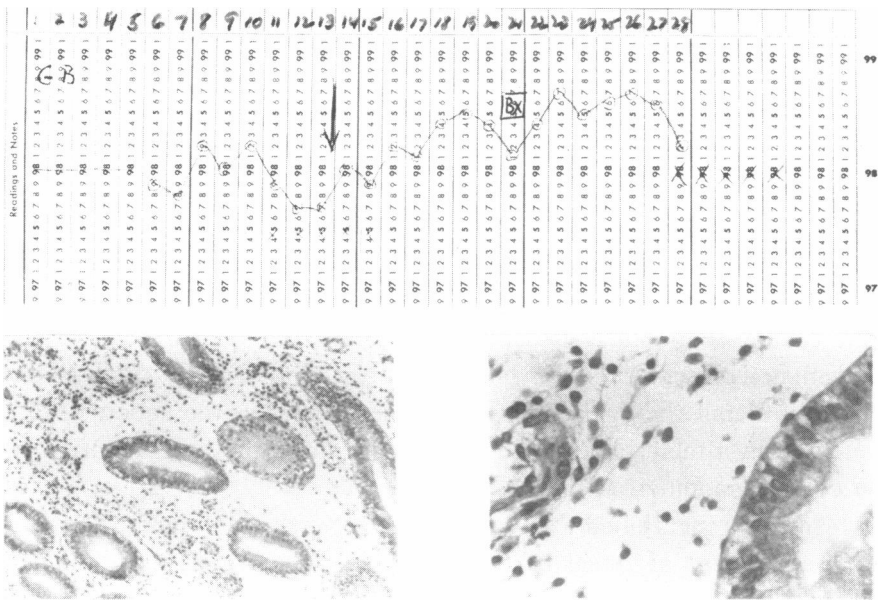

Fig. 5. Histologic features of luteal phase defect. M. G., 37-year-old para 1, with secondary infertility. Endometrial biopsy obtained on cycle day 21 revealed glands compatible with cycle day 17 and loose edematous stroma, compatible with cycle day 20-21.

life span of corpus luteum. In performing the biopsy at such times, there exists a remote chance of interrupting the pregnancy. However, one should obtain the biopsy from the anterior wall, and implantation usually occurs on the posterior uterine wall; therefore the chances of interrupting the pregnancy are really minimal. Hughes[12] reported statistical evidence for the therapeutic value of endometrial biopsy. In his infertility clinic more pregnancies occurred during the biopsy cycle than in other investigational cycles. He speculated that the decidual reaction could be induced from the increased vascularity due to the irritation of the biopsy.

During the past year we have inadvertently obtained three endometrial biopsies during the conception cycles. All pregnancies have not been disturbed.

Histological Features of Luteal Phase Defect

The most significant finding consists of a delay of two or more days in the development of secretory changes in the endometrium as

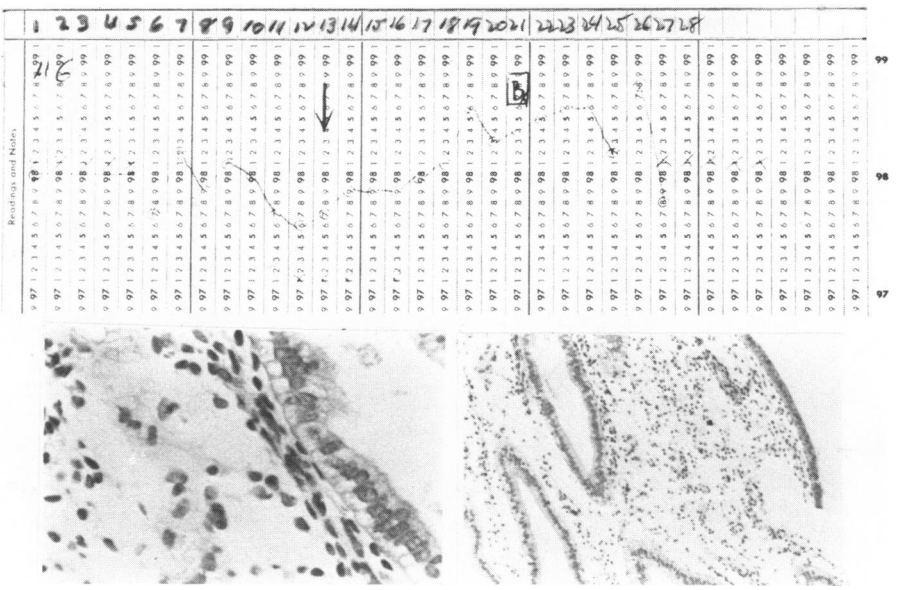

Fig. 6. Histologic features of luteal phase defect: 28-year-old female with primary infertility. Endometrial biopsy obtained on cycle day 21 showed retarded gland development compatible with cycle day 16, and more advanced, loose edematous stroma.

compared with cycle date. Characteristically, a discrepancy exists between the endometrial stroma, which appears somewhat more advanced, and the glands, which remain immature (Figures 5 and 6). It should again be emphasized that such findings must be documented in repeated cycles, since luteal disturbances may occur as isolated episodes, possibly even by a stressful situation of undergoing an infertility work-up.

Therapy of Luteal Phase Defect

The therapeutic approach can be based on two premises: substitution of deficient progesterone or stimulation of existing corpus luteum. The traditional substitution treatment, as advocated by Jones, utilizes progesterone per se rather than synthetic progestins. Progesterone has been found to be the most efficient drug in reproducing the normal physiologic progestational endometrial pattern in both glands and stroma. The most convenient mode of administration is by vaginal suppositories, 50 mg., given nightly after ovulation has occurred. If the desired therapeutic effect has not been produced, the mode of

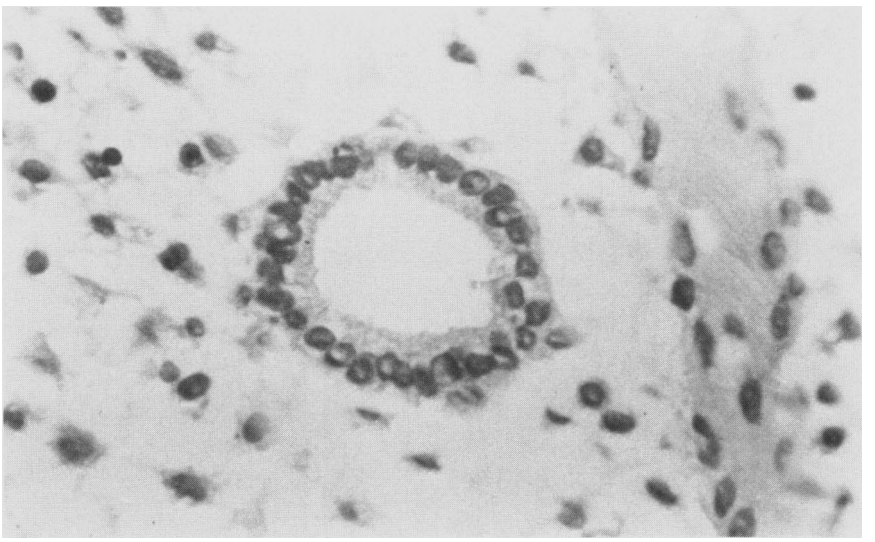

Fig. 7. Endometrial biopsy obtained after 16-day course of synthetic estrogen-progestogen combination: inactive, exhausted glands, edematous stroma.

administration is changed to daily IM injections of 12.5 mg. of progesterone in oil from the time of ovulation until the onset of menses. The dosages described have been found to be sufficient to cause secretory endometrial response, but not enough to produce a pseudopregnancy effect or to delay the menses. If the menstrual flow does not ensue a possibility of pregnancy is contemplated, the treatment with long-acting progestational agents is instituted, and the progress of gestation observed with quantitative HCG and pregnanediol assays.

If synthetic progestogens are used, a combination of drugs such as norethinodrel with mestranol (Enovid), norethindrone (Norlutin), or progestational agents alone, such as medroxyprogesterone (Provera) in doses of 5 to 10 mg. are given daily from cycle day 16 to 18 for seven to 10 days.

We had satisfactory therapeutic results utilizing Provera 10 mg. daily from cycle day 18 for seven days. If inadequate estrogenic endometrial priming is suspected, however, Enovid should be the drug of choice, or a combination of Provera with Premarin, 3.75 mg. It should be kept in mind that carrying the treatment beyond the recommended time limit or initiating it too early (before cycle day 18) might

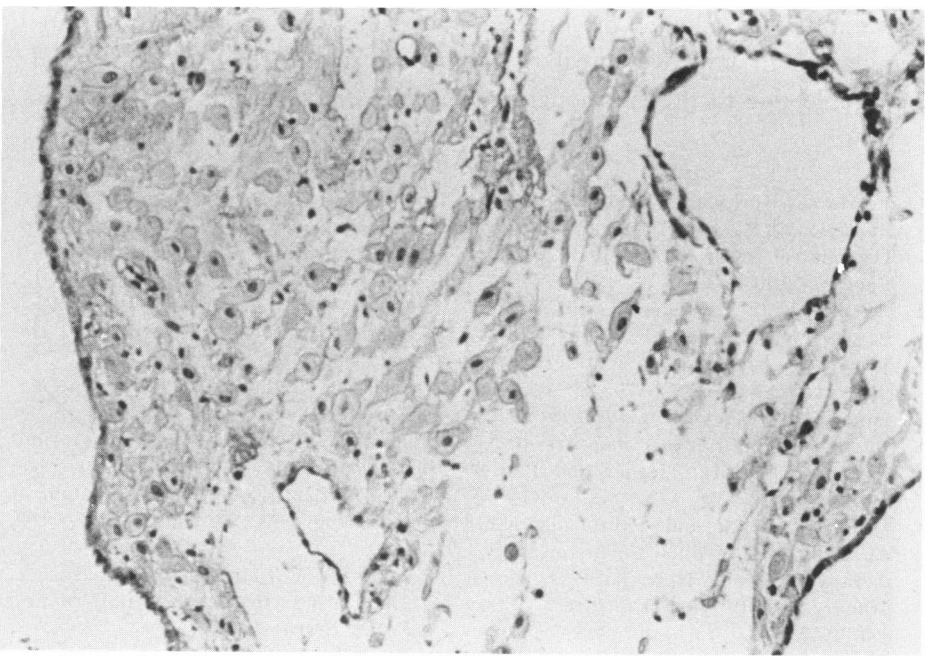

Fig. 8. Endometrial pseudopregnancy effect following administration of a long acting progestational agent (Delalutin).

reflect the deleterious effect of synthetic steroids on glandular epithelium, defeating the purpose of treatment (Figure 7). The use of long-acting progestins (Delalutin) is not recommended; the absorption curve of this drug is such that in order to produce a proper concentration at the desired time, it is necessary to administer initially the amount which might eventually produce a pseudopregnancy effect (Figure 8).

The rationale for stimulation treatment is based on the luteotrophic properties of HCG. An attempt to increase the secretion of endogenous progesterone may be made by giving 2,000 international units (IU) of human chorionic gonadotropin (A.P.L. Pregnyl) intramuscularly on the sixth and eighth postovulatory days, or in doses of 2,500 to 5,000 IU every three days from cycle day 12 to 24.

Our preference has been various modalities of substitution regimens, which usually result in an adequate therapeutic response; they are also simpler, easy to carry out, and are well accepted by patients. We

reserve HCG stimulation, however, for patients undergoing ovulation induction with Clomid or, on occasion, following artificial donor insemination to improve luteal performance, which theoretically could be altered due to the emotional tension and stress of such a procedure.

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